



NOTES FLAVIVIRUSES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Single-stranded, $\oplus$ -sense, enveloped RNA viruses
- AKA arboviruses
- > 40 types identified

Replication

- Cell surface attachment → cytoplasm entry → viral protein translation → viral RNA genome replication → virion formation (encapsidation) → cellular release

Transmission

- Primarily transmitted via arthropod bites

RISK FACTORS

- Recent endemic area travel/residence
- Poor insect repellent use
- Improper skin coverage (e.g. long sleeve clothing)

SIGNS & SYMPTOMS

- Mainly asymptomatic
- Others commonly have acute-onset flu-like symptoms
- Serious complications/sequelae commonly

characterized by neurologic disease (e.g. seizure, encephalopathy)

- Fever, nausea/vomiting

DIAGNOSIS

LAB RESULTS

- Serology
- Time-dependent on infection course, immune response
- Reverse transcription polymerase chain reaction (RT-PCR) for viral antigens

OTHER DIAGNOSTICS

- Endemic area travel/residence
- Presence of mosquito bite(s)

TREATMENT

- No cure

MEDICATIONS

- Variable vaccine availability
 - Untenable mainly due to antigenic mutations, multiple genotypes

OTHER INTERVENTIONS

- Fluid, electrolyte balance

VISIT...

LANZAROTE
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DENGUE VIRUS

osms.it/dengue-virus

PATHOLOGY & CAUSES

- Viral disease, mosquito transmission
 - Characterized by febrile illness
 - AKA break-bone fever
- Four serotypes
 - DENV-1 through DENV-4
 - IgG response to specific type → lifetime immunity
 - Limited, transient cross-protectivity across viral types
- Vector
 - Primarily *Aedes aegypti* and *A. albopictus*

Pathogenesis

- *Aedes* mosquito bite → dengue virus skin introduction → local infection, response → dissemination → viremia (2–6 days later) → circulating leukocyte infection (especially) monocytes → viral replication, release → fever

RISK FACTORS

- Endemic area residence
- Recent travel

COMPLICATIONS

Severe dengue

- AKA dengue hemorrhagic fever
- Viremia → local hemorrhage → systemic hemorrhage → hemodynamic collapse → shock
 - Dengue shock syndrome (rare complication—DENV-2 confers highest risk)
- Direct bone marrow infection → hematopoietic stem cell infection → ↓ megakaryocyte differentiation (among all other cell lines) → ↓ platelets formed
 - ↓ **Circulating lifetime**: virus-antibody complex → circulating platelet adherence → complement destruction

of virus-antibody complex → adherent platelet destruction

- Capillary leak
 - **Direct effect**: viral endothelial cell infection → cellular dysfunction → tight junction widening → capillary leak
 - **Indirect**: virus-infected monocytes, dendritic cells, mast cells → TNF- α , IFN- γ , IL-2, IL-8, vascular endothelial growth factor release, complement activation → ↑ capillary permeability
- Molecular mimicry
 - Viral E protein antibody response → plasminogen cross-reaction → inefficient coagulation cascade → hemorrhage
- Liver failure
 - Direct viral infection → Kupffer cells, hepatocytes → apoptosis → hepatocellular necrosis, Councilman bodies
 - Severe disease → shock → liver hypoperfusion → hepatocellular injury, death
- Central nervous system (CNS) involvement
 - Rare, direct viral infection of brain parenchyma

SIGNS & SYMPTOMS

- High-grade fever ($> 38.5^{\circ}\text{C}/101.3^{\circ}\text{F}$)
- Generalized pain
 - Abdominal pain/tenderness, headache, joint pain, muscle pain, eye/retro-orbital pain
- Nausea/vomiting
- Mucosal bleeding
- Rash

Severe symptoms and signs

- Severe bleeding
- Fluid accumulation → respiratory distress
 - Ascites, pleural effusion

- Neurologic impairment
 - Lethargy, seizure, encephalopathy

DIAGNOSIS

LAB RESULTS

- Leukopenia
- Thrombocytopenia
- ↑ Hematocrit

Antibody testing

- Antigen assay
 - $\oplus$ < five days of infection
- IgM
 - $\oplus$ $\geq$ three days of infection
- IgG
 - $\oplus$ $\geq$ seven days of infection
 - May be $\oplus$ due to prior infection

OTHER DIAGNOSTICS

Positive tourniquet test

- Blood pressure cuff insufflation → maintain pressure midway between systolic, diastolic → hold for five minutes → deflate → observe for petechiae
 - **Positive test:** 10+ petechiae in 2.5cm/1in

TREATMENT

MEDICATIONS

- No antiviral therapy available
- Fever control
 - Antipyretics

OTHER INTERVENTIONS

- Maintain adequate intravascular volume
- Shock
 - Crystalloid fluid resuscitation
- Bleeding
 - Platelet transfusion if severe thrombocytopenia and/or active, uncontrolled bleeding

Prevention

- Mosquito control
 - ↓ Standing water breeding sites
 - Copepod use (organisms feed on mosquito larvae)
 - Insecticides
- Personal protective measures
 - Repellant use
 - Permethrin-treated clothing (Na⁺ channel blockade → neurotoxicity → paralysis → death; low toxicity in humans)

WEST NILE VIRUS

osms.it/west-nile-virus

PATHOLOGY & CAUSES

- Virus causing mosquito-borne, self-limited disease
 - Characterized by flu-like symptoms
 - Potential for severe neurologic sequelae
- Vector
 - *Culex* mosquito

Pathogenesis

- *Culex* mosquito bite → viral replication in skin's dendritic cells → lymph node migration → further replication →

enters bloodstream → visceral organ dissemination

- Complication arise when virus enters bloodstream → crosses blood-brain barrier

Transmission

- Infected bird (amplifying host) → prolonged viremia → *Culex* mosquito blood meal → human/other vertebrate bite → blood meal, virus-laden saliva injected → virus transmission
- Viral-load organ/blood donation
- Transplacental infection

RISK FACTORS

- Elderly
- Immunosuppressed individuals
- Malignancy (especially hematologic malignancies)
- Chemokine receptor CCR5 deficiency
 - Chemokine involved in viral infection immune response (especially brain parenchyma)

COMPLICATIONS

- Neurological
 - Meningitis, encephalitis, tremor, flaccid paralysis, Guillain-Barré syndrome
- Ocular
 - Chorioretinitis, uveitis, optic neuritis
- Cardiac
 - Myocarditis, cardiac arrhythmias
- Muscular
 - Myositis, rhabdomyolysis
- Other
 - Pancreatitis, orchitis, hepatitis, central diabetes insipidus

SIGNS & SYMPTOMS

- Abrupt-onset fever, headache, myalgias
 - Usual presentation is self-limited (AKA West Nile Fever)
- Abdominal pain, anorexia, nausea/vomiting, diarrhea, maculopapular rash

Neurologic complications

- Motor
 - Tremor, flaccid paralysis (Guillain-Barré complications)
- Meningoencephalitis
 - Meningismus, altered mental status

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Neurologic sequelae → ↑ signal in T2 imaging

Nerve action potentials

- Normal sensory conduction velocity
- Abnormally ↓ motor neuron velocity, potentials

LAB RESULTS

- Reverse transcription polymerase chain reaction (RT-PCR)
- Viral cultures
- Cerebrospinal fluid
 - Severe cases
 - If present in CSF → neuroinvasive disease likely
 - Neutrophilic pleocytosis (<500 cells/microL) → lymphocytic predominance as disease progresses
 - ↑ Protein (<150mg/dl)
- Serology
 - Enzyme-linked immunosorbent assay (MAC-ELISA) for IgM detection → positive 4-10 days after viremia detection

OTHER DIAGNOSTICS

- Integument examination
 - Maculopapular rash
- Neurological
 - Meningismus (in severe cases)

Electroencephalography (EEG)

- Generalized, continuous slowing prominent in frontal/temporal regions

TREATMENT

- No cure

OTHER INTERVENTIONS

Prevention

- Personal protection measures
- Mosquito control programs
- Blood donor screening

YELLOW FEVER VIRUS

osms.it/yellow-fever-virus

PATHOLOGY & CAUSES

- Virus that causes mosquito-borne illness in endemic, tropical areas (Africa, South America)
 - Characterized by hemorrhagic fever, coagulopathy, shock (most severe cases)
- Seven major genotypes, conserved in each specific endemic region
 - Only one serotype that has remained antigenically conserved
- Vector
 - *Aedes*, *Haemagogus* mosquitoes

Pathogenesis

- Female *Haemagogus* mosquito bite → viral transmission → skin dendritic cells infected → lymphatic spread → monocyte/macrophages, histiocytes in lymph node → replication → lymphatic, hematogenous spread throughout body
 - 3–6 day incubation period until symptoms appear

Transmission

- Infected monkey → *Haemagogus* mosquito bite → human bite → blood meal, viral transmission
- During epidemics/urban spread
 - *Aedes* mosquito feeds on infected humans → infected *Aedes* mosquito → feeds on another human → viral transmission

COMPLICATIONS

- Hepatic injury → viral hepatitis
 - **Councilman bodies** (hepatocytes characterized by eosinophilic degeneration with condensed nuclear chromatin) present on histology
 - **Jaundice** results
 - Severe disease → ↓ vitamin

K-dependent coagulation factors → hemorrhagic diathesis

- Shock
 - Due to cytokine dysregulation
 - ↑ IL-1, IL-6, TNF-alpha, IFN-10
- Renal failure
 - Hypotension/hepatorenal syndrome → eosinophilic degeneration, renal parenchyma fatty change
- Hemorrhage
- Secondary bacterial infection
- Myocardial infection

Neurological

- Delirium, convulsions, coma

SIGNS & SYMPTOMS

- Infection period (3–4 days)
 - Acute-onset headache, **fevers**, chills, myalgia
 - Photophobia, restlessness, anorexia, **vomiting**
- Remission period (up to 48 hours)
 - Afebrile
 - No other symptoms

Severe yellow fever

- Intoxication period (3–6 days after infection onset)
- Nausea/**vomiting**, **fever**, oliguria → anuria, epigastric tenderness, jaundice
- Hemorrhage
 - **Coffee-ground emesis**, melena, hematuria, petechiae, ecchymoses
- Myocardial injury
 - Cardiac enlargement, conduction abnormalities
- Neurological dysfunction
 - Altered mental status, convulsions, delirium

DIAGNOSIS

LAB RESULTS

- Renal dysfunction
 - Azotemia, proteinuria, creatinine (3--8x normal value)
- PCR
 - Viral genome
- CSF analysis
 - ↑ opening pressure, ↑ protein, ⊖ cells

Serology

- Enzyme-linked immunosorbent assay (ELISA)
 - IgM antibodies
- Reverse-transcriptase loop-mediated isothermal amplification (RT-LAMP)
 - Field test for quick diagnostics
 - Easy-to-read visual test, good sensitivity

OTHER DIAGNOSTICS

ECG

- Cardiac conduction abnormalities
- ST-T abnormalities

TREATMENT

OTHER INTERVENTIONS

- Fluid management, resuscitation
- Bleeding diathesis reversal
 - Fresh frozen plasma
- Adequate nutrition

Prevention

- Live attenuated vaccine
 - Recommended for individuals > nine months old residing in/traveling to endemic areas
 - Contraindication in children < six months old
- Passive maternal immunization
 - Safest immunoglobulin transfer

ZIKA VIRUS

osms.it/zika-virus

PATHOLOGY & CAUSES

- Mosquito-borne virus
 - Characterized by mild disease in infected individuals, serious neurologic sequelae in developing fetus
- Vector
 - Aedes aegypti/albopictus mosquitoes

Pathogenesis

- Aedes mosquito bite → dendritic cell infection, replication → bloodstream → dissemination
- Maternal infection → placental injury → fetus infection → neuronal progenitor cell infection → neuronal cell death

Transmission

- Human-to-human close contact

- E.g. sexual contact
- Possible transmission via other bodily secretions (e.g. tears, sweat) in individuals with very high viral loads
- Blood transfusion
- Organ transplantation
- Maternal-fetal spread

COMPLICATIONS

- Microcephaly in developing newborns
- Greatest risk for sequelae estimated to occur with first, second trimester infection
 - Serious neurological, intellectual deficits
 - Seizures
 - Vision, hearing problems
- Neurological sequelae
 - Guillain-Barré syndrome
 - Myelitis

- Meningoencephalitis

SIGNS & SYMPTOMS

- Mild fever
- Maculopapular rash
- Nonpurulent conjunctivitis
- Joint, muscle pain

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Pregnant individuals
 - Microcephaly, growth retardation evaluation

LAB RESULTS

- RT-PCR
 - If < 14 days from symptoms onset
 - Confirmatory testing with plaque reduction neutralization test (PRNT)
 - PRNT: measure of antibodies that neutralize virus-specific antigens

Serology

- IgM against Zika virus
 - If > 14 days from onset of symptoms

TREATMENT

- No cure

MEDICATIONS

- Antipyretics

OTHER INTERVENTIONS

Mother

- Rest
- Fluid management, resuscitation

Newborn

- Nutritional support
- Physical therapy
- Specialty referral (especially neurology)

Prevention

- No vaccine available
- Personal protective measures in endemic areas
- Consultation with physician prior to travel for pregnant individuals
- Safe sexual practice
 - Biologically-male individuals wait at least six months after endemic-area travel for unprotected sex
 - Biologically-female individuals wait at least eight weeks after endemic-area travel for unprotected sex
- Blood donation
 - Do not donate for at least six months after endemic-area travel

FLAVIVIRUSES OVERVIEW

	MOSQUITO VECTOR	DEFINING SIGNS/SYMPTOMS	VACCINE?
DENGUE	<i>Aedes aegypti</i> and <i>albopictus</i>	High fever; hemorrhage → shock	No
WEST NILE	<i>Culex</i>	Fever, headache, myalgias; severe neurologic sequelae	No
YELLOW FEVER	<i>Aedes species</i> and <i>haemagogus</i>	Fever, chills, myalgia; hemorrhage, neurologic sequelae, hepatitis	Yes
ZIKA	<i>Aedes aegypti</i> and <i>albopictus</i>	Adult: mild fever, rash Prenatal: microcephaly, severe neurologic compromise	No